IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Constance A. Bell et al.	Art Unit	: 1637
Serial No.	: 10/068,238	Examiner	: Teresa E. Strzelecka
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Title	: DETECTION OF BACILLUS ANTHRACIS		

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BRIEF ON APPEAL

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(5) Summary of Claimed Subject Matter

Independent claim 57 is directed toward articles of manufacture that comprise a pair of *capB* primers, a pair of *capB* probes, and a donor fluorescent moiety and a corresponding acceptor fluorescent moiety (see, for example, page 12, lines 5-11, and page 16, line 25 to page 17, line 15). The pair of *capB* primers includes a first *capB* primer consisting of the sequence 5'-CCC AAT TCG AGT AAA CAT A-3' (SEQ ID NO:1) and a second *capB* primer consisting of the sequence 5'- ACT GCC ATA CAT TCA CAA -3' (SEQ ID NO:2), and the pair of *capB* probes includes a first *capB* probe consisting of the sequence 5'- CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC -3' (SEQ ID NO:3) and a second *capB* probe consisting of the sequence 5'- GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG -3' (SEQ ID NO:4) (see, for example, page 12, line 12 to page 13, line 6 and Table 1 at page 28).

Independent claim 70 is directed toward articles of manufacture that comprise a pair of *pagA* primers, a pair of *pagA* probes, and a donor fluorescent moiety and a corresponding acceptor fluorescent moiety (see, for example, page 12, lines 5-11, and page 16, line 25 to page 17, line 15). The pair of *pagA* primers includes a first *pagA* primer consisting of the sequence 5'-TAC AGG ACG GAT TGA TAA G-3' (SEQ ID NO:5) and a second *pagA* primer consisting of the sequence 5'- TTT CAG CCC AAG TTC TTT -3' (SEQ ID NO:6), and the pair of *pagA* probes includes a first *pagA* probe consisting of the sequence 5'- AGT ACA TGG AAA TGC AGA AGT G -3' (SEQ ID NO:7) and a second *pagA* probe consisting of the sequence 5'- ATG CGT CGT TCT TTG ATA TTG GT -3' (SEQ ID NO:8) (see, for example, page 12, line 12 to page 13, line 6 and Table 1 at page 28).

Independent claim 83 is directed toward articles of manufacture that comprise a pair of *lef* primers, a pair of *lef* probes, and a donor fluorescent moiety and a corresponding acceptor fluorescent moiety (see, for example, page 12, lines 5-11, and page 16, line 25 to page 17, line 15). The pair of *lef* primers includes a first *lef* primer consisting of the sequence 5'-TTT TAC CGA TAT TAC TCT CC-3' (SEQ ID NO:9) and a second *lef* primer consisting of the sequence 5'- AAC CTA AAG GCT TCT GC -3' (SEQ ID NO:10), and the pair of *lef* probes includes a first *lef* probe consisting of the sequence 5'- ATT AAG GAA TGA TAG TGA GGG T -3' (SEQ ID NO:11) and a second *lef* probe consisting of the sequence 5'- TAT ACA CGA ATT TGG

ACA TGC T -3' (SEQ ID NO:12) (see, for example, page 12, line 12 to page 13, line 6 and Table 1 at page 28).

Independent claim 96 is directed toward an article of manufacture that comprises a pair of *capB* primers, a pair of *capB* probes, a pair of *pagA* primers, a pair of *pagA* probes, a pair of *lef* primers, and a pair of *lef* probes (see, for example, page 5, lines 1-30). The pair of *capB* primers includes a first *capB* primer consisting of the sequence 5'-CCC AAT TCG AGT AAA CAT A-3' (SEQ ID NO:1) and a second *capB* primer consisting of the sequence 5'-ACT GCC ATA CAT TCA CAA-3' (SEQ ID NO:2), and the pair of *capB* probes includes a first *capB* probe consisting of the sequence 5'-CGA TTA AGC GCC GTA AAG AAG GTC CTA ATA TC-3' (SEQ ID NO:3) and a second *capB* probe consisting of the sequence 5'-GTG AGC AAC GCA GGG TAG TTA AAG AGG CTG-3' (SEQ ID NO:4) (see, for example, page 12, line 12 to page 13, line 6 and Table 1 at page 28). The pair of *pagA* primers includes a first *pagA* primer consisting of the sequence 5'-TAC AGG ACG GAT TGA TAA G-3' (SEQ ID NO:5) and a second *pagA* primer consisting of the sequence 5'-TTT CAG CCC AAG TTC TTT-3' (SEQ ID NO:6), and the pair of *pagA* probes includes a first *pagA* probe consisting of the sequence 5'-AGT ACA TGG AAA TGC AGA AGT G- 3' (SEQ ID NO:7) and a second *pagA* probe consisting of the sequence 5'-ATG CGT CGT TCT TTG ATA TTG GT- 3' (SEQ ID NO:8) (see, for example, page 12, line 12 to page 13, line 6 and Table 1 at page 28). The pair of *lef* primers includes a first *lef* primer consisting of the sequence 5'-TTT TAC CGA TAT TAC TCT CC-3' (SEQ ID NO:9) and a second *lef* primer consisting of the sequence 5'-AAC CTA AAG GCT TCT GC-3' (SEQ ID NO:10), and the pair of *lef* probes includes a first *lef* probe consisting of the sequence 5'-ATT AAG GAA TGA TAG TGA GGG T- 3' (SEQ ID NO:11) and a second *lef* probe consisting of the sequence 5'-TAT ACA CGA ATT TGG ACA TGC T- 3' (SEQ ID NO:12) (see, for example, page 12, line 12 to page 13, line 6 and Table 1 at page 28).

(7) Arguments

(A) The rejection of claims 57, 66 and 67 under 35 U.S.C. §103(a).

For the following reasons, the combination of cited references does not render obvious independent claim 57 and dependent claims 66 and 67.

First, the Examiner asserted that all primers and probes are equivalent and cited the Buck et al. reference to support this assertion. Buck et al. is a reference disclosing that a number of different sequencing primers were used successfully to sequence a particular target nucleic acid. The results of Buck et al., however, were not based on amplification reactions, did not use *capB* nucleic acid sequences, and did not even use *B. anthracis* nucleic acid sequences. Even ignoring the fact that Buck et al. does not use *B. anthracis* nucleic acid as the template, an automated sequencing reaction is significantly different from, for example, a PCR amplification reaction in which at least two oligonucleotides generally are used, or a real-time PCR amplification reaction in which at least four oligonucleotides generally are used. The results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions because, as Applicants have repeatedly argued, primer design for PCR amplification and primer and probe design for real-time PCR amplification is not always predictable.

In fact, Applicants have provided evidence of the unpredictability of primer and probe design. Significantly, and contrary to the Examiner's assertions, the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility state that one should "…be aware that no set of guidelines will always accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well."[1] In addition to the University of Chicago DNA Sequencing Facility guidelines, Applicants have made of record a number of peer-reviewed publications that compare different primer sets or compare the same primer set under different amplification conditions. For example:

[1] http://cancer-seqbase.uchicago.edu/primers.html (Exhibit H)

- the Csordas et al. reference[2] states that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those specifically designed for real-time PCR"[3] (see, the Abstract);
- the Elnifro et al. reference[4] states that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (see, the first full sentence at page 560);
- the Tichopad et al. reference[5] states that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see, the Abstract); and
- the Abd-Elsalam reference[6] states that "…the most critical parameter for successful PCR is the design of primers" (see, the first full paragraph at page 94).

These references support Applicants' assertion that all primers and probes are not equivalent and may not work in an amplification reaction. It is noteworthy that a number of these references were published after Applicants' 2001 priority date, indicating that the state of the art, even after the present application was filed, was such that primer and probe design was not predictable.

Applicants' arguments are consistent with the Courts' recent decisions under 35 U.S.C. §103. Under the obviousness standard recently clarified by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*[7], such evidence of unpredictability strongly argues against the Examiner's obviousness rejections. As held by the Supreme Court in *KSR*:

> When there are a *finite* number of identified, *predictable* solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated* success, it is likely the product not of innovation but of ordinary skill and common sense (emphasis added).

Such is not the case in the present application; the "known options" in the prior art are not "finite, identified, and predictable". In addition, none of the cited references, alone or in combination, provide the "anticipated success" referred to in *KSR*. As stated by the Court in

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[2] Csordas et al. (2004) *Lett. App. Microbiol.* 39:187-193 (Exhibit I)
[3] For the convenience of the Board, Applicants note that end-point PCR corresponds to conventional PCR and utilizes two primers while real-time PCR utilizes two primers and two probes.
[4] Elnifro et al. (2000) *Clin. Microbiol. Rev.* 13:559-570 (Exhibit J)
[5] Tichopad et al. (2004) *Mol. Cell. Probes* 18:45-50 (Exhibit K)
[6] Abd-Elsalam (2003) *African J. Biotech.* 2:91-95 (Exhibit L)
[7] *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007)

Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.[8], "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."

To further support the rejection, the Examiner asserted that the claimed primer and probe sequences represent "structural homologs" of prior art sequences, and the Examiner cited *In re Deuel* to support this assertion. That is, according to the Examiner, the *capB* oligonucleotide sequences disclosed by Ramisse et al. are "structural homologs" of the presently claimed primer and probe sequences, even though Ramisse et al. does not disclose any of the presently claimed sequences. Contrary to the Examiner's assertion, *In re Deuel* does not indicate that two oligonucleotides that have different sequences but are complementary to the same target sequence are "structural homologs." *In re Deuel* held that claimed nucleic acid sequences were not obvious over prior art references that disclosed partial amino acid sequences encoded by such nucleic acid sequences and, therefore, *In re Deuel* is not germane to claims reciting specific nucleotide sequences such as those in the present case.

In addition, *In re Deuel* does not indicate that a primer or probe sequence that is complementary to a portion of a larger sequence is a "structural homolog," and Applicants are aware of no case law that stands for the proposition that a longer sequence makes *per se* obvious specific primer and probe sequences from within that longer sequence. Applicants understand that a longer sequence can be viewed as representing a very large genus of possible sub-sequences from which appropriate primers and probes can be selected. However, based on current case law, each of the claimed primer and probe sequences is not obvious over sequences disclosed in the cited references, and the particular combinations of four sequences that are claimed are certainly not obvious over sequences disclosed in the cited references. See, for example, *In re Bell*,[9] in which the Court held that "given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious." Further, the

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[8] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364, 86 USPQ2d 1196 (Fed. Cir. 2008)

[9] *In re Bell* 991, F.2d 781, 784, 26 USPQ2d 1529 (Fed. Cir. 1993)

lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

As the Board is aware, a number of decisions, including those discussed herein, indicate that a species (e.g., a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length *capB* sequence disclosed in Makino et al.). Applicants note that much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species (sometimes referred to as an "invention of selection") is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*,[10] in which the Court stated that "a gene is a chemical compound." As such, independent claim 57 requires a combination of four different specific chemical species.

Applicants believe the record amply supports the argument of nonobviousness. However, objective evidence of nonobviousness, which, according to *Ortho-McNeil v. Mylan*[11], "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness", also has been provided. For example, the sequences recited in the present claims exhibit high sensitivity and specificity toward their targets. See, for example, Examples 1, 4, and 5 of Applicants' specification. In addition, the claimed probe sequences (SEQ ID NOs: 3 and 4) each have a particular melting temperature that was identified and is disclosed in the specification. The particular melting temperatures can be used as confirmation of the presence or absence of *B. anthracis* in a sample. Therefore, the claimed probe sequences can be used to further increase the accuracy of detecting *B. anthracis*. See, for example, page 23, lines 5-7 and Example 3 of the specification. Thus, the exceptional sensitivity and specificity of the claimed combinations was unexpected. According to *KSR*[12], 35 U.S.C. §103 does not bar patentability where, as here, the claimed invention presents an unpredictable variation of the prior art and operates in an "unexpected and fruitful manner."

In summary, Courts have long held that species (in the present case, the specific oligonucleotides recited in the pending claims) are not obvious over a very large genus (in the

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[10] *Amgen, Inc. v.Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016 (Fed. Cir. 1991)
[11] *Supra* at 1365
[12] *Supra* at 1740

present case, the full-length *capB* sequence disclosed by Makino et al.). Applicants also have provided evidence that, even after the application was filed, there was unpredictability in primer and probe design, particularly for PCR and real-time PCR reactions. Given the disclosures of Ramisse et al. and Makino et al., one of ordinary skill in the art would not have been able to predictably modify the disclosed sequences, even in view of Buck et al., to arrive at the claimed combination of two primers and two probes having the ability to specifically amplify and detect *B. anthracis* DNA by real-time PCR as do the claimed primers and probes. Further, Applicants have provided independent evidence in the form of secondary considerations that render the claims nonobvious.

Thus, for at least the reasons set forth herein, the primer and probe sequences recited in present claims 57, 66 and 67 are not obvious over the combination of cited references. Accordingly, Applicants respectfully request that the Board overturn the rejection of these claims under 35 U.S.C. §103(a).

(B) The rejection of claims 70, 79 and 80 under 35 U.S.C. §103(a).

For the following reasons, the combination of cited references does not render obvious independent claim 70 and dependent claims 79 and 80.

As with the rejection above, the Examiner asserted that all primers and probes are equivalent and cited the Buck et al. reference to support this assertion. Buck et al. is a reference disclosing that a number of different sequencing primers were used successfully to sequence a particular target nucleic acid. The results of Buck et al., however, were not based on amplification reactions, did not use *pagA* nucleic acid sequences, and did not even use *B. anthracis* nucleic acid sequences. Even ignoring the fact that Buck et al. does not use *B. anthracis* nucleic acid as the template, an automated sequencing reaction is significantly different from, for example, a PCR amplification reaction in which at least two oligonucleotides generally are used, or a real-time PCR amplification reaction in which at least four oligonucleotides generally are used. The results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions because, as Applicants have repeatedly argued, primer design for

PCR amplification and primer and probe design for real-time PCR amplification is not always predictable.

As discussed herein, Applicants have provided evidence of the unpredictability of primer and probe design in the form of the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility, which states that one should "…be aware that no set of guidelines will always accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well."[13] Also as discussed herein, Applicants have made of record a number of peer-reviewed publications that compare different primer sets or compare the same primer set under different amplification conditions. For example:

- the Csordas et al. reference[14] states that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those specifically designed for real-time PCR"[15] (see, the Abstract);
- the Elnifro et al. reference[16] states that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (see, the first full sentence at page 560);
- the Tichopad et al. reference[17] states that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see, the Abstract); and
- the Abd-Elsalam reference[18] states that "…the most critical parameter for successful PCR is the design of primers" (see, the first full paragraph at page 94).

These references support Applicants' assertion that all primers and probes are not equivalent and may not work in an amplification reaction. It is noteworthy that a number of these references were published after Applicants' 2001 priority date, indicating that the state of the art, even after the present application was filed, was such that primer and probe design was not predictable.

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[13] *Supra*
[14] *Supra*
[15] For the convenience of the Board, Applicants note that end-point PCR corresponds to conventional PCR and utilizes two primers while real-time PCR utilizes two primers and two probes.
[16] *Supra*
[17] *Supra*
[18] *Supra*

Applicants' arguments herein are consistent with the Courts' recent decisions under 35 U.S.C. §103. Under the obviousness standard recently clarified by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*[19], such evidence of unpredictability strongly argues against the Examiner's obviousness rejections. As held by the Supreme Court in *KSR*:

> When there are a *finite* number of identified, *predictable* solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated* success, it is likely the product not of innovation but of ordinary skill and common sense (emphasis added).

Such is not the case in the present application; the "known options" in the prior art are not "finite, identified, and predictable". In addition, none of the cited references, alone or in combination, provide the "anticipated success" referred to in *KSR*. As stated by the Court in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*[20], "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."

In addition, the Examiner asserted that the claimed primer and probe sequences represent "structural homologs" of prior art sequences, and the Examiner cited *In re Deuel* to support this assertion. That is, according to the Examiner, the *pagA* oligonucleotide sequences disclosed by Ramisse et al. are "structural homologs" of the presently claimed primer and probe sequences, even though Ramisse et al. does not disclose any of the presently claimed sequences. Contrary to the Examiner's assertion, *In re Deuel* does not indicate that two oligonucleotides that have different sequences but are complementary to the same target sequence are "structural homologs." *In re Deuel* held that claimed nucleic acid sequences were not obvious over prior art references that disclosed partial amino acid sequences encoded by such nucleic acid sequences and, therefore, *In re Deuel* is not germane to claims reciting specific nucleotide sequences such as those in the present case.

In re Deuel does not indicate that a primer or probe sequence that is complementary to a portion of a larger sequence is a "structural homolog," and Applicants are aware of no case law that stands for the proposition that a longer sequence makes *per se* obvious specific primer and

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[19] *Supra*
[20] *Supra* at 1364

probe sequences from within that longer sequence. Applicants understand that a longer sequence can be viewed as representing a very large genus of possible sub-sequences from which appropriate primers and probes can be selected. However, based on current case law, each of the claimed primer and probe sequences is not obvious over sequences disclosed in the cited references, and the particular combinations of four sequences that are claimed are certainly not obvious over sequences disclosed in the cited references. See, for example, *In re Bell*,[21] in which the Court held that "given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious." Further, the lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

As the Board is aware, a number of decisions, including those discussed herein, indicate that a species (e.g., a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length *pagA* sequence disclosed in Price et al.). As already noted, much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species (sometimes referred to as an "invention of selection") is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*,[22] in which the Court stated that "a gene is a chemical compound." As such, independent claim 70 requires a combination of four different specific chemical species.

Applicants believe the record amply supports the argument of nonobviousness. However, objective evidence of nonobviousness, which, according to *Ortho-McNeil v. Mylan*[23], "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness", also has been provided. For example, the sequences recited in the present claims exhibit high sensitivity and specificity toward their targets. See, for example, Examples 1, 4, and 5 of Applicants' specification. In addition, each of the claimed probe sequences (SEQ ID NOs: 7 and 8) has a particular melting temperature that was identified

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[21] *Supra* at 784
[22] *Supra* at 1206
[23] *Supra* at 1365

and is disclosed in the specification. The particular melting temperatures can be used as confirmation of the presence or absence of *B. anthracis* in a sample. Therefore, the claimed probe sequences can be used to further increase the accuracy of detecting *B. anthracis*. See, for example, page 23, lines 5-7 and Example 3 of the specification. Thus, the exceptional sensitivity and specificity of the claimed combinations was unexpected. According to *KSR*[24], 35 U.S.C. §103 does not bar patentability where, as here, the claimed invention presents an unpredictable variation of the prior art and operates in an "unexpected and fruitful manner."

In summary, Courts have long held that species (in the present case, the specific oligonucleotides recited in the pending claims) are not obvious over a very large genus (in the present case, the full-length *pagA* sequence disclosed in Price et al.). Applicants also have provided evidence that, even after the application was filed, there was unpredictability in primer and probe design, particularly for PCR and real-time PCR reactions. Given the disclosures of Ramisse et al. and Price et al., one of ordinary skill in the art would not have been able to predictably modify the disclosed sequences, even in view of Buck et al., to arrive at the claimed combination of two primers and two probes having the ability to specifically amplify and detect *B. anthracis* DNA by real-time PCR as do the claimed primers and probes. Further, Applicants have provided independent evidence in the form of secondary considerations that render the claims nonobvious.

Thus, for at least the reasons set forth herein, the primer and probe sequences recited in present claims 70, 79 and 80 are not obvious over the combination of cited references. Accordingly, Applicants respectfully request that the Board overturn the rejection of these claims under 35 U.S.C. §103(a).

(C) The rejection of claims 83, 92 and 93 under 35 U.S.C. §103(a).

For the following reasons, the combination of cited references does not render obvious independent claim 83 and dependent claims 92 and 93.

As with the rejection above, the Examiner asserted that all primers and probes are equivalent and cited the Buck et al. reference to support this assertion. Buck et al. is a reference

[24] *Supra* at 1740

disclosing that a number of different sequencing primers were used successfully to sequence a particular target nucleic acid. The results of Buck et al., however, were not based on amplification reactions, did not use *lef* nucleic acid sequences, and did not even use *B. anthracis* nucleic acid sequences. Even ignoring the fact that Buck et al. does not use *B. anthracis* nucleic acid as the template, an automated sequencing reaction is significantly different from, for example, a PCR amplification reaction in which at least two oligonucleotides generally are used, or a real-time PCR amplification reaction in which at least four oligonucleotides generally are used. The results reported by Buck et al. using sequencing primers are not representative of results using different primer and probe sequences in various types of amplification reactions because, as Applicants have repeatedly argued, primer design for PCR amplification and primer and probe design for real-time PCR amplification is not always predictable.

As discussed herein, Applicants have provided evidence of the unpredictability of primer and probe design in the form of the guidelines published by the University of Chicago Cancer Research Center DNA Sequencing Facility, which states that one should "…be aware that no set of guidelines will always accurately predict the success of a primer. Some primers may fail for no apparent reason, and primers that appear to be poor candidates may work well."[25] Also as discussed herein, Applicants have made of record a number of peer-reviewed publications that compare different primer sets or compare the same primer set under different amplification conditions. For example:

- the Csordas et al. reference[26] states that "[p]rimers originally designed for end-point PCR did not have adequate specificity or sensitivity compared with those specifically designed for real-time PCR"[27] (see, the Abstract);
- the Elnifro et al. reference[28] states that "[e]mpirical testing and a trial-and-error approach may have to be used when testing several primer pairs, because there are no means to predict the performance characteristics of a selected primer pair even among those that satisfy the general parameters of primer design" (see, the first full sentence at page 560);
- the Tichopad et al. reference[29] states that "unknown tissue-specific factors can influence amplification kinetics but this affect can be ameliorated, in part, by appropriate primer selection" (see, the Abstract); and

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[25] *Supra*
[26] *Supra*
[27] For the convenience of the Board, Applicants note that end-point PCR corresponds to conventional PCR and utilizes two primers while real-time PCR utilizes two primers and two probes.
[28] *Supra*
[29] *Supra*

- the Abd-Elsalam reference[30] states that "…the most critical parameter for successful PCR is the design of primers" (see, the first full paragraph at page 94).

These references support Applicants' assertion that all primers and probes are not equivalent and may not work in an amplification reaction. It is noteworthy that a number of these references were published after Applicants' 2001 priority date, indicating that the state of the art, even after the present application was filed, was such that primer and probe design was not predictable.

Applicants' arguments herein are consistent with the Courts' recent decisions under 35 U.S.C. §103. Under the obviousness standard recently clarified by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*[31], such evidence of unpredictability strongly argues against the Examiner's obviousness rejections. As held by the Supreme Court in *KSR*:

> When there are a *finite* number of identified, *predictable* solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the *anticipated* success, it is likely the product not of innovation but of ordinary skill and common sense (emphasis added).

Such is not the case in the present application; the "known options" in the prior art are not "finite, identified, and predictable". In addition, none of the cited references, alone or in combination, provide the "anticipated success" referred to in *KSR*. As stated by the Court in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*[32], "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."

In addition, the Examiner asserted that the claimed primer and probe sequences represent "structural homologs" of prior art sequences, and the Examiner cited *In re Deuel* to support this assertion. That is, according to the Examiner, the *lef* oligonucleotide sequences disclosed by Ramisse et al. are "structural homologs" of the presently claimed primer and probe sequences, even though Ramisse et al. does not disclose any of the presently claimed sequences. Contrary to the Examiner's assertion, *In re Deuel* does not indicate that two oligonucleotides that have different sequences but are complementary to the same target sequence are "structural

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[30] *Supra*
[31] *Supra* at 1742
[32] *Supra* at 1364

homologs." *In re Deuel* held that claimed nucleic acid sequences were not obvious over prior art references that disclosed partial amino acid sequences encoded by such nucleic acid sequences and, therefore, *In re Deuel* is not germane to claims reciting specific nucleotide sequences such as those in the present case.

In re Deuel does not indicate that a primer or probe sequence that is complementary to a portion of a larger sequence is a "structural homolog," and Applicants are aware of no case law that stands for the proposition that a longer sequence makes *per se* obvious specific primer and probe sequences from within that longer sequence. Applicants understand that a longer sequence can be viewed as representing a very large genus of possible sub-sequences from which appropriate primers and probes can be selected. However, based on current case law, each of the claimed primer and probe sequences is not obvious over sequences disclosed in the cited references, and the particular combinations of four sequences that are claimed are certainly not obvious over sequences disclosed in the cited references. See, for example, *In re Bell*,[33] in which the Court held that "given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities [to select], the claimed sequences would not have been obvious." Further, the lack of motivation to select a particular DNA sequence from among numerous degenerate variants was a factor in determining the non-obviousness of the claims in *In re Deuel*.

As the Board is aware, a number of decisions, including those discussed herein, indicate that a species (e.g., a particular oligonucleotide) is not obvious over a very large genus (in this case, all possible fragments of the full-length *lef* sequence disclosed in Bragg et al.). Applicants note that much of the case law regarding the non-obviousness of a species over the prior art teaching of a genus containing such a species (sometimes referred to as an "invention of selection") is in the chemical arts. Significantly, the Courts have stated in several major opinions that DNA is a chemical. See, for example, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*,[34] in which the Court stated that "a gene is a chemical compound." As such, independent claim 83 requires a combination of four different specific chemical species.

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[33] *Supra* at 784
[34] *Supra* at 1206

Applicants believe the record amply supports the argument of nonobviousness. However, objective evidence of nonobviousness, which, according to *Ortho-McNeil v. Mylan*[35], "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness", also has been provided. For example, the sequences recited in the present claims exhibit high sensitivity and specificity toward their targets. See, for example, Examples 1, 4, and 5 of Applicants' specification. In addition, the claimed probe sequences (SEQ ID NOs: 11 and 12) has a particular melting temperature that was identified and is disclosed in the specification. The particular melting temperatures can be used as confirmation of the presence or absence of *B. anthracis* in a sample. Therefore, the claimed probe sequences can be used to further increase the accuracy of detecting *B. anthracis*. See, for example, page 23, lines 5-7 and Example 3 of the specification. Thus, the exceptional sensitivity and specificity of the claimed combinations was unexpected. According to *KSR*[36], 35 U.S.C. §103 does not bar patentability where, as here, the claimed invention presents an unpredictable variation of the prior art and operates in an "unexpected and fruitful manner."

In summary, Courts have long held that species (in the present case, the specific oligonucleotides recited in the pending claims) are not obvious over a very large genus (in the present case, the full-length *lef* sequence disclosed in Bragg et al.). Applicants also have provided evidence that, even after the application was filed, there was unpredictability in primer and probe design, particularly for PCR and real-time PCR reactions. Given the disclosures of Ramisse et al. and Bragg et al., one of ordinary skill in the art would not have been able to predictably modify the disclosed sequences, even in view of Buck et al., to arrive at the claimed combination of two primers and two probes having the ability to specifically amplify and detect *B. anthracis* DNA by real-time PCR as do the claimed primers and probes. Further, Applicants have provided independent evidence in the form of secondary considerations that render the claims nonobvious.

Thus, for at least the reasons set forth herein, the primer and probe sequences recited in present claims 83, 92 and 93 are not obvious over the combination of cited references.

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[35] *Supra* at 1365
[36] *Supra* at 1740

Accordingly, Applicants respectfully request that the Board overturn the rejection of these claims under 35 U.S.C. §103(a).

(D) The rejection of claim 96 under 35 U.S.C. §103(a).

Claim 96 is directed toward an article of manufacture that includes all four *capB* primers and probes (SEQ ID NOS:1-4), all four *pagA* primers and probes (SEQ ID NOS:5-8), and all four *lef* primers and probes (SEQ ID NOS:9-12).

The Ramisse et al., Makino et al., Price et al., Bragg et al., and Buck et al. references are discussed above. None of these references teaches or suggests any of the *twelve* specific primer or probe sequences recited in claim 96. The arguments herein regarding the Examiner's assertions with respect to *In re Deuel* and "structural homologs" are reiterated with respect to the rejection of this claim.

Applicants fail to understand how a claim reciting *twelve* very specific primer and probe sequences to three different gene targets can be obvious over the cited art. As indicated herein, a combination of four claimed primer and probe sequences (i.e., combination of four different specific chemical species) is not obvious over the cited references, and certainly not the particular combination of *twelve* primer and probe sequences recited in claim 96.

In addition, as indicated herein, Applicants have presented evidence of secondary considerations with respect to the unexpectedly high sensitivity and specificity of the presently claimed primers and probes.

Accordingly, Applicants respectfully request withdrawal of the rejection of claim 96 under 35 U.S.C. § 103(a).